ORIGINAL PAPERS

Clinical status, quality of life, and work productivity in Crohn's disease patients after one year of treatment with adalimumab

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ABSTRACT

Objective: Clinical trials have shown the efficacy of adalimumab in Crohn's disease, but the outcome in regular practice remains unknown. The aim of the study was to examine clinical status, quality of life, and work productivity of Crohn's disease patients receiving adalimumab for one year in the context of usual clinical practice.

Material and methods: This was a prospective, observational study with a one-year follow-up. After baseline, Crohn's disease patients were evaluated at 1, 3, 6, 9, and 12 months after starting treatment with adalimumab. Outcome variables included: clinical status (measured with CDAI), quality of life (measured with EuroQoL-5D and IBDQ), and work productivity (measured with WPAI questionnaire). These outcome variables were compared using the Student's t test or Wilcoxon test for paired comparison data according to the data distribution. Statistical significance was set at two-sided $p < 0.05$.

Results: The sample was composed of 126 patients (age [mean] 39.1 ± [standard deviation] 13.8 years; 51% male). Significant changes were observed during the follow-up period: CDAI decreased from [median] 194 ([25-75 percentiles] 121-269) to 48.2 (10.1-122.0) ($p < 0.05$); the EuroQoL-5D increased from 0.735 (0.633-0.790) to 0.797 (0.726-1.000) ($p < 0.05$); the EuroQoL-5D visual analogue scale increased from 50.0 (40-70) to 80.0 (60-90); ($p < 0.05$) and the IBDQ increased from 56.7 (51.6-61.5) to 67.5 (60.1-73.6) ($p < 0.05$). The total work productivity impact decreased from 53% to 24% ($p < 0.05$).

Conclusions: In regular practice, adalimumab is clinically effective in the treatment of Crohn's disease patients and results in a significant improvement in quality of life and work productivity.

Key words: Adalimumab. Crohn's disease. IBD. Quality of life. Work productivity.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory illness characterized by periods of remission and exacerbation which may involve any area of the gastrointestinal tract. Past studies have estimated CD incidence rate in Europe between 2.5 and 7.5 cases/100,000 inhabitants/year (1-3); however, the rate has been increasing in recent years, with the latest estimates being around 9 cases/100,000 inhabitants/year (4-7). CD is usually diagnosed during young adulthood, and the mortality rate, although higher than that of the overall population, is not very high. Thus, patients are affected mostly by CD-related morbidity and treatment for most of their lives, with the corresponding impact on their health-related quality of life (HRQoL) and work productivity.

There is clear evidence of the negative impact of CD on HRQoL. Cohen, in a recent meta-analysis of 22 articles, concluded that HRQoL is worse in CD patients than in healthy controls and patients with ulcerative colitis, and similar to that of other chronic diseases. HRQoL levels also worsen with higher disease activity (8). Studies of CD in Spain report evidence of a high impact of the disease on overall wellbeing, social function and vitality; a moderate impact on emotional function, psychological function, and physical pain; and a mild impact on physical function (9).

In addition to generic measurement tools such as the EuroQoL-5D or the SF-36, there are specific instruments to assess quality of life in CD patients such as the commonly used Inflammatory Bowel Disease Questionnaire (IBDQ), with a 36-item version (10) and a 9-item version (11).

There are also studies that show the negative impact of CD on work productivity and activity impairment (12). A version of the assessment tool Work Productivity and Activity Impairment questionnaire (WPAI) has been adapted specifically for CD (13-15) and validated in Spain (16,17).

With regard to treatment, new therapies have emerged, such as those referred to as biological treatments. These treatments include elements (usually monoclonal antibodies) designed to block certain molecules involved in the inflammatory response or the corresponding receptors in cell membranes. Biological compounds have revolutionized the therapeutic approach to CD, especially for those patients with severe or refractory disease. A recent meta-analysis of clinical trials concluded that biological treatments are effective for the induction of remission of active CD and the prevention of flare-ups (18). Clinical trials have also reported improvements in work productivity (19,20) and quality of life (21-23).

The objective of this study was to examine these reported associations in regular clinical practice, *i.e.,* outside the controlled environment of a clinical trial. Thus, our aim was to measure the improvement in clinical health status, quality of life, and work productivity in CD patients who are naïve to biological therapy for one year after starting treatment with adalimumab in the context of regular practice.

MATERIALS AND METHODS

This is an observational cohort study with a prospective (one year follow-up) and retrospective design. This work is part of the larger study named Efficacy of Adalimumab in Crohn's Disease (EFICA-DEC is the acronym in Spanish).

Baseline data, collected during the first visit (V0), included socio-demographic information, CD history, clinical status and quality of life at V0, and information on work activity during the previous week and previous year. During the five following visits at months 1, 3, 6 ,9, and 12 from baseline (V1, V2, V3, V4, and V5, respectively), data collected included clinical data, quality of life, and work and non-work activity information for the week prior to the visit. We included CD patients who are naïve to any biological treatment for whom adalimumab treatment was prescribed as part of regular clinical practice. Exclusion criteria included incomplete clinical records for the 12 months prior to the start of treatment with adalimumab and any anti-TNF treatment prior to the start of adalimumab therapy.

We calculated that a sample size of 100 patients was required to detect differences in the CDAI mean of 100 points, assuming a standard deviation of 250 ($\alpha = 0.05$; $\beta = 0.2$). To achieve this final sample size, it was necessary to recruit 132 patients into the study based on an attrition rate between 25% and 36% observed in the CHARM study (24).

The outcome variables under study included: clinical variables, quality of life and work productivity measures at the different clinical visits. The following instruments collected the relevant data: Crohn's Disease Activity Index (CDAI) (25) assessed clinical status (proportion of patients with CDAI < 150, in remission, and global score); Perianal Disease Activity Index (PDAI), or Irvine PDAI (26) (remission is defined as a baseline value > 0 and a value = 0 for items 1, 2, 3, and 5, at the end of the one year treatment). Other outcome variables of interest included: corticoid tapering rate and, at the end of the study period, changes in quality of life as measured by EuroQoL-5D (the descriptive system index ranging from 0 to 1 and the visual analog scale [VAS] from 0 to 100) (27), and by IBDQ-9 (normalized scale from 0 to 100) (11). Finally, impact on work productivity and activity impairment was measured with the WPAI adapted to CD (17), which evaluates four different aspects of CD impact on work productivity during the previous seven days: percentage of lost work hours (absenteeism), percentage of impact on hours worked (presenteeism), percentage of total work productivity impact (TWPI: absenteeism and presenteeism combined), and percentage of impact on activity outside work.

Missing values in outcome variables (CDAI, PDAI, IBDQ and EuroQoL-5D) were replaced via an imputation method. We imputed the predicted values based on the slope of the regression line drawn between the value of the previous visit and the value of the subsequent visit, adjusted for time. For those cases where there was no visit following that with the missing data, the missing value was replaced with the value of the previous visit.

In the descriptive analysis, qualitative or categorical variables were expressed in percentages. Quantitative variables were tested for normality; if the variable was normally distributed, we described it by its mean and standard deviation (mean ± SD). Hypothesis testing for these variables was performed with the Student's t test for paired data. For variables not normally distributed we reported the median and the interquartile range (median [P25-P75]). Hypotheses contrasts involving these variables were tested using the Wilcoxon tests for paired data. For bivariate analyses Pearson's Chi-squared statistic or Fisher's exact test when there were five or fewer observations in a category were used. Statistical significance was set at two-sided $p < 0.05$.

RESULTS

A total of 132 patients were recruited from 33 centers located in 11 geographical regions. Of these 132 records, six were eliminated due to incomplete data. For the total

of five visits for each of the remaining 126 patients, eight missing values had to be imputed in CDAI, ten values in IBDQ, and seven in EuroQoL-5D. Of the 33 patients with perianal disease, 25 PDAI missing values were imputed. Forty-three patients presented a CDAI < 150 at study entry.

Socio-demographic characteristics

Women made up almost half the sample population (49.2%), the mean age was 39.1 ± 13.8 years, and patients had been diagnosed with CD over a median of seven years (RIC 3-12). At diagnosis, 25 patients (19.8%) presented with extraintestinal manifestations and another 25 had perianal involvement. At baseline (V0), 76 patients (60.3%) were in the labor force, of which 51.3% had been on sick leave in the previous year. Among those on sick leave in the previous year due to CD, the median number of days off work was 53 (13.5-120).

Clinical status at baseline

Table I shows the clinical status of CD patients at baseline (V0). Based on the Montreal classification by location of the disease, 35.7% of CD was in L1; 10.3%, in L2; 47.6%, in

L3; 2.4%, in L4; 3.2%, in L1 + L4; and 0.8%, in L2 + L4. In terms of disease behavior, 46.8% of patients presented an inflammatory pattern, 15.9% presented a stenotic pattern, and 11.1% presented a fistulizing pattern. At baseline, there were 33 patients (26.2%) with perianal involvement, and 33 patients presented extraintestinal manifestations as well.

Adalimumab regimen

As a first induction dose, 85.7% of patients received 160 mg of adalimumab and another 13.5% received 80 mg. The second induction dose consisted of 80 mg for 86.5% of patients and 40 mg for 13.5%. Throughout the study, a maintenance dose of 40 mg was administered every 15 days in 92% of cases.

Response to treatment

Table II shows response to adalimumab treatment data according to clinical criteria. At V1 (one month into treatment) complete response (CR) was observed in 55.6% of cases, partial response (PR) was seen in 42.1%, and treatment had to be discontinued in 2.4% of patients. By the end of the 12 months of treatment (V5), CR was 67.7%, PR

Table I. Characteristics of Crohn's disease patients at baseline (visit 0) (n = 126)

		n	%
Location according to Montreal classification	L1: Terminal ileum	45	35.7
	L2: Colon	13	10.3
	L3: Ileocolic	60	47.6
	L4: Upper digestive tract	3	2.4
	L1 + L4	4	3.2
	L2 + L4	1	0.8
Clinical pattern according Montreal classification	B1: Inflammatory	59	46.8
	B2: Stenotic	20	15.9
	B3: Fistulizing	14	11.1
	B1p: B1 + perianal	24	19.0
	B2p: B2 + perianal	4	3.2
	B3p: B3 + perianal	5	4.0
Extraintestinal manifestations	Yes	33	26.2
Reasons for indicating treatment with adalimumab	Severe initial flare	2	1.6
	Intolerance to immunosuppressors	24	19.0
	Luminal disease resistant to immunosuppressors	76	60.3
	Perianal disease resistant to immunosuppressors	13	10.3
	Bridge to immunosuppressors	4	3.2
	Extraintestinal manifestations	7	5.6

Table II. Response to adalimumab treatment and reasons for cessation at different times of the study

	Visit 1 (n = 126)		Visit 2 (n = 126)		Visit 3 (n = 125)		Visit 4 (n = 123)		Visit 5 (n = 124)	
Response to treatment (n = 126)	n	%	n	%	n	%	n	%	n	%
Complete	70	55.6	84	66.7	81	64.8	86	69.9	84	67.7
Partial	53	42.1	33	26.2	32	25.6	18	14.6	18	14.5
Cessation	3	2.4	9	7.1	12	9.6	19	15.4	22	17.7
Reasons for cessation										
Lack of response	0	0.0	4	44.4	8	66.7	10	52.6	11	50.0
Adverse effects	1	33.3	2	22.2	2	16.7	5	26.3	7	31.8
Other	2	66.7	3	33.3	2	16.7	4	21.1	4	18.2

was 14.5%, and treatment was discontinued for 17.7% of patients. Approximately one third of treatment cessations, both at V1 as well as at V5, were due to adverse effects. By the end of the follow-up, half of the treatment interruptions were caused by a lack of response to adalimumab. Corticoid tapering rate during follow-up was 87.4%, although in two cases where the patients had not taken corticoids in the previous year treatment with corticoids had to be reintroduced. CDAI changes throughout the study period are shown in figure 1 and table III. The proportion of patients in remission increased significantly from V0 to V1 (34.1% vs 78.6%) (p < 0.001), with a moderate increase until reaching 83.3% by the end of follow-up (Fig. 1). CDAI global score decreased significantly (p < 0.05) in each consecutive visit from V0 to V3, after which changes were no longer statistically significant. During the entire period, the median score decreased from 194 (121-269) to 48.2 (10.1-122) (Table III). At V1, 57.9% of patients had improved 70 or more points compared to their V0 score, and 45.2% had improved 100 or more points. At six months of treatment (V3) these percentages were 65.1%
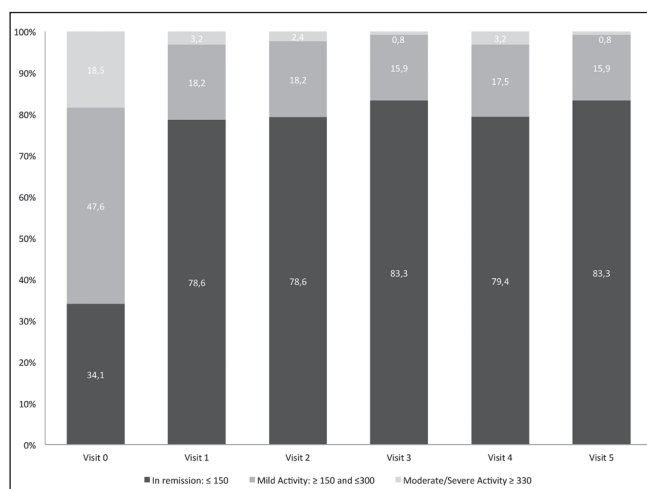
and 57.9%, respectively, and at 12 months of treatment (V5) these proportions held at 69.8% and 58.7%, respectively.

Regarding the 33 patients with perianal disease at study entry, the last follow-up PDAI was available for 29, of which ten (34.4%) experienced remission of the perianal disease. Table IIIA shows that the global score for the index decreased from 4 (2-8) to 0 (0-3.5) (p < 0.05). It is worth noting that each of the intermediate differences in scores, *i.e.,* between baseline and each of the following visits, was also statistically significant.

Quality of life and work and social impact

Table IIIB shows the results regarding quality of life. Here we observed that the median for EuroQoL-5D increased from a baseline value of 0.735 (0.633-0.790) to 0.797 (0.726-1.000) (p < 0.05) after 12 months on adalimumab. Again, the changes between V0 and each of the following visits were also statistically significant. The corresponding VAS increased from 50.0 (40-70) at V0 to 80.0 (60-90) at V5 (p < 0.05). The global score for the IBDQ increased significantly from 56.7 (51.6-61.5) at V0 to 64.7 (59.4-72.1) at V1, and continued to improve until V2 (67.5; 60.6-72.1), maintaining these gains by the end of the 12 months (67.5; 60.1-73.6) (p < 0.05). Figure 2 shows that the evolution of the EuroQoL-5D VAS was more gradual and substantive than that for IBDQ. As part of the WPAI test results we observed that CD-caused absenteeism decreased significantly from V1 until the end of follow-up, almost one third of patients reported a percentage > 50% at V0 but, by their last visit (V5), under one tenth of patients reported percentages > 50%. A similar evolution was detected for presenteeism and, consequently, for TWPI (absenteeism and presenteeism combined). TWPI diminished significantly from V1 until the end of the study; at V0 over half of all patients reported a TWPI of 50% but by V5 only one fifth of them were as high. Percentage of impact of CD on regular activity outside

Fig. 1. Distribution of patients according to CDAI scores by visit (n = 126).

Table III. A. Clinical changes from visit 0 to visit 5 (V0-V5) measured with CDAI (n = 126) and PDAI (n = 33).
B. Changes in quality of life assessed with EuroQoL-5D and IBDQ-9 (n = 126)

A

CDAI Global score (range 0-600)	V0	V1	V2	V3	V4	V5
Mean (SD)	197.5 (102.5)	100.1 (79.3)	86.0 (85.1)	77.4 (82.1)	78.1 (92.9)	70.3 (75.5)
Median (P25-P75)	194.0 (121.0-269.0)	82.1 (46.9-137.0)	66.3 (25.6-127.0)	50.9 (24.1-118.3)	50.1 (8.8-119.8)	48.2 (10.1-121.9)
p < 0.05 in visits:	V1, V2, V3, V4, V5	V0, V2, V3, V4, V5	V0, V1, V3, V4, V5	V0, V1, V2	V0, V1, V2	V0, V1, V2
PDAI global score (range 0-20)						
Mean (SD)	5.3 (4.5)	2.6 (2.8)	1.9 (2.1)	1.7 (2.1)	1.8 (2.6)	1.8 (2.7)
Median (P25-P75)	4.0 (2.0-8.0)	2.0 (0.0-4.0)	2.0 (0.0-3.0)	1.0 (0.0-3.0)	0.0 (0.0-3.0)	0.0 (0.0-3.5)
p < 0.05 in visits:	V1, V2, V3, V4, V5	V0	V0	V0	V0	V0

B

EuroQoL-5D index (range 0-1)	V 0	V1	V2	V3	V4	V 5
Mean (SD)	0.680 (0.228)	0.785 (0.200)	0.800 (0.208)	0.813 (0.203)	0.805 (0.238)	0.815 (0.214)
Median (P25-P75)	0.735 (0.633-0.790)	0.790 (0.684-1.000)	0.797 (0.726-1.000)	0.795 (0.735-1.000)	0.799 (0.707-1.000)	0.797 (0.726-1.000)
p < 0.05 in visits:	V1, V2, V3, V4, V5	V0	V0	V0	V0	V0
EuroQoL-5D VAS (range 0-100)						
Mean (SD)	55.6 (19.8)	67.2 (19.9)	71.6 (17.6)	74.5 (18.8)	70.9 (22.6)	72.1 (21.8)
Median (P25-P75)	50.0 (40.0-70.0)	70.0 (50.0-80.0)	70.0 (60.0-85.0)	80.0 (60.0-90.0)	75.0 (60.0-90.0)	80.0 (60.0-90.0)
p < 0.05 in visits:	V1, V2, V3, V4, V5	V0, V2, V3, V4, V5	V0, V1, V3	V0, V1, V2, V4	V0, V1, V3	V0, V1
IBDQ-9 Index (range 0-100)						
Mean (SD)	57.5 (7.7)	65.1 (8.9)	66.5 (8.9)	66.6 (9.1)	67.3 (9.0)	67.6 (9.5)
Median (P25-P75)	56.7 (51.6-61.5)	64.7 (59.4-72.1)	67.5 (60.6-72.1)	66.5 (60.8-73.6)	66.5 (60.1-73.6)	67.5 (60.1-73.6)
p < 0.05 in visits:	V1, V2, V3, V4, V5	V0, V3, V4, V5	V0	V0, V1	V0, V1	V0, V1

IBDQ-9: 9-item Inflammatory Bowel Disease Questionnaire; VAS: Visual Analog Scale; CDAI: Crohn's Disease Activity Index; PDAI: Perianal Disease Activity Index or Irvine PDAI. Values between visits were compared using Wilcoxon test for paired data.

work exhibited a very similar pattern to that of the global work productivity pattern.

DISCUSSION

Our results indicate that adalimumab, as administered in regular clinical practice in a scheduled regimen, is highly effective on CD from the first month of treatment, and this effect persists for at least an entire year.

Regarding response to treatment, our results show that a CR peak is reached at about three months into treatment (V2)

and this level remains more or less constant for the rest of the follow-up. In case of maintained partial response, clinicians opted for treatment suspension. Treatment was stopped in 1 of every 5 to 6 patients. Over half of the time the decision to stop was due to a lack of response, and in one third of the cases treatment cessation was due to adverse effects.

All outcome variables (CDAI, PDAI, EuroQoL-5D, IBDQ, WPAI) experience a statistically significant improvement after the first month of treatment with adalimumab. Improvement tends to continue after this first spurt but at a slower pace (and not always with statistically significant changes) up to visit 2 or 3 (at three or six months,
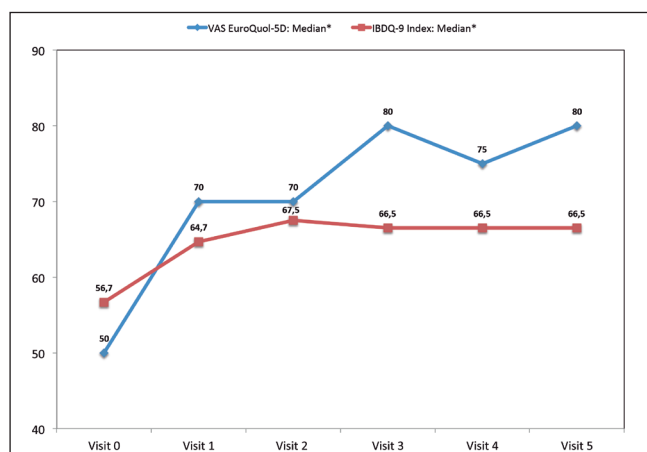
Fig. 2. Changes in quality of life.

respectively). After this, gains are maintained, and became stable through to the end of the follow-up period. In a previous study with infliximab in patients with active CD, a similar pattern was found with significant improvement at four weeks in quality of life and the CDAI. This improvement remained at week 8 (28).

The percentage of patients in total remission according to CDAI increased by 49% at six months, mirroring data reported in the CHARM study (22). Specifically, this study reported a 40% increase in patients receiving a regimen of 40 mg of adalimumab every two weeks and a 47% increase among those on a weekly regimen. It is worth mentioning that the percentage of patients improving by ≥ 100 and ≥ 70 in the first six months from V0 (65.1% and 57.9%, respectively) was slightly greater than the numbers reported in CHARM (51.7% and 54.1% on bimonthly regimen, respectively, and 52.2% and 56.1% on a weekly regimen).

Because CD is usually diagnosed during young adulthood (30.1 ± 13.6 year-olds), this disease has a substantial impact on the patient work life by requiring a considerable amount of sick leave. Adalimumab reduced the number of lost work hours and work productivity due to CD considerably as early as one month after the start of treatment. Our results differ slightly from those presented in other studies on the effects of adalimumab on work productivity. One meta-analysis (29) concluded that after one year of treatment the weighted average of improvement for absenteeism was 8.7% (range: 7.2%-10.3%), 22.2% for presenteeism (range: 18.2%-26.1%), and 24.9% for TWPI (range: 20.0%-29.7%) *versus* our weighted averages of 21.7%, 16.8% and 29.1%, respectively. In the CHOICE (30) study, carried out in CD patients treated with adalimumab after failure of infliximab, 8% of patients improved with regard to absenteeism, as well as 15% and 18% in presenteeism and TWPI, respectively. These results in the multicenter study CARE (20) are 9.6%, 17.3% and 18.4% respectively. The most striking finding of our results, in relation to these previous studies, is the value of absenteeism at baseline (32%) *versus* 15% in CHOICE (30) and

23% in CARE (20). These variations may be explained away by the different work environments in the different countries where the studies were carried out, as well as by differences in patient profiles. In our study, absenteeism is greater but presenteeism is lower, which translates into a smaller difference in the total measure of work productivity, TWPI. Regarding the impact on *activity outside work score* in the CHOICE (30) study, an improvement of around 20% was obtained at four weeks after starting adalimumab treatment, remaining stable for the rest of the year. However, in our study, the period of improvement of this score is longer (until week 12), reaching a greater improvement (27%) and then remaining stable.

Our results regarding quality of life (EuroQoL index) are also slightly different from those reported by Yu et al. (31) based on patients with moderate-severe CD. In this study, Yu et al. compared the efficacy of adalimumab and infliximab and found that the quality of life after 12 months of treatment with adalimumab (measured with the EuroQoL-5D index) was somewhat higher than our results (0.865 and 0.815, respectively). However, they failed to report the improvement recorded during the first 12 months of treatment, which reached 0.135 in our sample. Other studies, using different instruments for measuring quality of life, obtained findings consistent with ours in terms of quality of life improvement (30,32).

Our results should be interpreted in the context of the study limitations. The main limitation of the EFICADEC study in general is the inherent difficulty of extracting retrospective data from patient clinical history of the year prior to baseline. However, all analyses for this work were based exclusively on prospective data collected via validated questionnaires filled out during the subsequent visits, thus we expect these data to be highly reliable. Another limitation could derive from imputing missing data on the global scores for CDAI, EuroQoL-5D, IBDQ, and PDAI. Despite this, the number of data imputed was very low (1.2% [8/630] in CDAI; 1.1% [7/630] in EuroQoL-5D; 1.6% [10/630] in IBDQ, and 6.0% [25/165] in PDAI). These low percentages combined with the method used to calculate the imputed value (regression imputation based on the previous and following observations to the missing data; in the absence of the following value, the missing value was replaced with that of the previous visit) minimize the possibility of biasing the results.

Based on our results, we draw the following conclusions:

1. Patients on adalimumab showed improvements in clinical measures (CDAI, PDAI) similar to those reported in clinical trials. These improvements are noticeable from the first month of treatment and progressive up to three or six months of treatment, when it reaches its peak and stabilizes until the end of the study period of one year.
2. After the one-year treatment, over 50% of patients stop taking corticoids.

3. The impact of adalimumab on work productivity is significant and substantial. How presenteeism and absenteeism evolve in our study is slightly different than those in previous studies, though the behavior of TWPAI is similar to that found in these studies.
4. HRQoL, measured with EuroQoL-5D and IBDQ, improves substantially from the onset of adalimumab treatment and gains remain stable throughout the follow-up period.

CONFLICT OF INTEREST AND FUNDING

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